REMARKS

These remarks are in response to the final Office Action mailed April 7, 2004. Claim 25 has been added. The amendment introduces no new matter. Claims 1-25 are pending.

A. Rejection Under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 12, 14, 16-18, and 20-24 have been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which allegedly was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. This rejection is respectfully traversed.

The burden of demonstrating that the claims are allegedly not supported by an adequate written description is squarely on the Examiner, as required by *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976). MPEP specifically states that a strong presumption of adequacy of written description exists and directs that § 112, paragraph 1 rejections of an original claim should be rare. MPEP §§ 2163(I)(A) and 2163(II)(A). It is respectfully submitted that in this case the Examiner has not met this burden.

The legal standard for determining the adequacy of written description is clear and well established. The description is adequate if "the disclosure of the application relied upon reasonably conveys to the artisan that the inventor had possession at [the time of filing] of the later claimed subject matter." *Wang Labs Inc. v. Toshiba Corp.*, 993 F.2d 858, 26 USPQ2d 1767. In other words, the question of the lack of adequate written description does not arise unless "one skilled in the art [would not be able] to immediately envisage the product claimed..." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 USPQ2d 1895. It is submitted that applying these broad principles to the present

application, it can be unequivocally concluded that the written description in this application adequately supports the claims.

More particularly, the Examiner has asserted (item 8, page 3 of the Office Action) that the compound R*(F—L—X) is claimed broadly, while the specification is "narrow in scope" (page 4, second paragraph of the Office Action), and thus the specification allegedly contains insufficient written description to support the entire scope of the pending claims. The Examiner based his conclusion, with which the Applicants respectfully disagree, on the following specific grounds.

(1) First, the Examiner asserted that the specification allegedly contains no "distinguishing structural attributes" for the moieties "X" and "R." The Examiner is mistaken. The specification lists a large number of these moieties as described below. But even if the specification listed only just a few "X" and "R" moieties, it would be still sufficient because it is well established law that the "written description requirement may be satisfied through sufficient description of a representative number of species..." *University of California v. Eli Lilly and Co.*, 119 F.3d at 1568, 43 USPQ2d at 1406 (Fed. Cir. 19970. And to be "adequate," the description of a "representative number of species" does not have to provide individual support for each species in the genus. *In re Bell,* 991 F.2d 781, 785 26 USPQ2d 1529, 1532 (Fed. Cir. 1993).

The Examiner clearly recognized (page 3, last paragraph and page 4, second paragraph of the Office Action), that at least some "X" and "R" moieties are described in the specification. In fact, a large number of these moieties is described, which undoubtedly qualifies as a "representative number." With regard to the ligand moieties "X," the Applicants direct the Examiner's attention to paragraph [0088] of the originally filed specification (pages 21-22), which provides the following non-limiting examples of the ligands "X" that can be used:

> "biotin, deiminobiotin, dethiobiotin, vicinal diols, such as 1,2-dihydroxyethane, 1,2-dihydroxycyclohexane, etc., digoxigenin, maltose, oligohistidine, glutathione, 2,4-dinitrobenzene, phenylarsenate, ssDNA, dsDNA, a peptide of polypeptide, a metal chelate, a saccharide, rhodamine or fluorescein, or any hapten to which an antibody can be generated ..."

With regard to the "R" moieties, the Applicants direct the Examiner's attention to paragraph [0086] of the originally filed specification (page 21), which provides the following non-limiting examples of the "R" moieties that can be used:

> "for example, a sulfonate ester can have R as any group, such as alkyl, heterocyclic, such as pyridyl, substituted pyridyl, imidazole, pyrrole, thiophene, furan, azole, oxazole, aziridine, etc., aryl, substituted aryl, amino acid or peptidyl, oligonucleotide or carbohydrate group"

In view of the foregoing, it is submitted that it cannot be reasonably maintained that the specification contains no "distinguishing structural attributes" for the moieties "X" and "R."

(2) Second, the Examiner asserted that the specification is allegedly narrow in scope because it disclosed "only one "non-directed library" of activity based probes" and identified this library as "eleven members of biotinylated sulfonate esters ... useful in identifying one target protein ... class I aldehyde dehydrogenase..." (page 4, second paragraph of the Office Action). The Examiner is mistaken.

With respect to the allegation that only one library of the probes has been described, the Applicants point out that as discussed in the previous communication, those skilled in the art recognize that each probe will vary depending upon the target protein. Thus, it cannot be said that only one library is taught in the specification,

because the ability to label proteins based on the activity is a true characteristic of a probe. Combining this characteristic with the information provided in the specification on how to select the target proteins and with the information on the functional groups of the probes in their relation to various targets, is clearly sufficient to demonstrate possession of the claimed invention.

More specifically, the Applicants direct the Examiner's attention to paragraph [0084] of the originally filed specification (page 20), which provides a large number of examples of functional groups F, thus rebutting the Examiner's assertion that the disclosure is limited only to biotinylated sulfonate esters group:

> "Exemplary Fs as used in an ABP of the invention include an alkylating agent, acylating agent, ketone, aldehyde, sulphonate or a phosphorylating agent. Examples of particular Fs include, but are not limited to fluorophosphonyl, fluorophosphoryl, fluorosulfonyl, alpha-haloketones or aldehydes or their ketals or acetals, respectively, alpha-haloacyls, nitriles, sulfonated alkyl or aryl thiols, iodoacetylamide group, maleimides, sulfonyl halides and esters, isocyanates, isothiocyanates, tetrafluorophenyl esters, N-hydroxysuccinimidyl esters, acid halides, acid anhydrides, unsaturated carbonyls, alkynes, hydroxamates, alpha-halomethylhydroxamates, aziridines, epoxides, or arsenates and their oxides. Sulfonyl groups may include sulfonates, sulfates, sulfinates, sulfamates, etc., in effect, any reactive functionality having a sulfur group bonded to two oxygen atoms. Epoxides may include aliphatic, aralkyl, cycloaliphatic and spiro epoxides, the latter exemplified by fumagillin, which is specific for metalloproteases."

Finally, the Applicants respectfully point out that particular examples of the probes provided in the specification (including examples) are merely illustrative and not intended to be limiting, and it is so stated in the specification.

With respect to the allegation that only one target protein has been described, the Applicants direct the Examiner's attention to paragraph [0075] of the originally filed specification (page 16):

> "Exemplary protein targets described herein include enzymes, included in the groups oxidoreductases, hydrolases, ligases, isomerases, transferases, and lyases and include such enzymes or enzyme groups as serine hydrolases, metallo-hydrolases, dehydrogenases, e.g. alcohol and aldehyde dehydrogenases, and nucleotide triphosphate (NT)-dependent enzymes, although, the invention envisions ABPs which recognize any protein, e.g., enzyme, family. Other proteins include proteins that bind to each other or to nucleic acids, such as transcription factors, kringle structure containing proteins, nucleic acid binding proteins, G-protein binding receptors, cAMP binding proteins, etc."

The specification also discloses other targets such as "enzymes, other proteins include receptors, transcription factors, G-proteins, and the like" (page 17, paragraph [0076]), and also describes with particularity the kinds of enzymes that can be used (page 32, paragraph [0115]).

In view of the foregoing, the Applicants submit that the present specification contains a complete description of the invention sufficient to demonstrate that the Applicants, at the time the application was filed, had possession of the claimed invention. Accordingly, it is respectfully submitted that the rejection of claims 12, 14, 16-18, and 20-24 under 35 U.S.C. § 112, first paragraph, as allegedly lacking adequate written description, is not properly applied. Reconsideration and withdrawal of the rejection are therefore respectfully requested.

B. Rejection Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 12, 14, 16-18, and 20-24 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is respectfully traversed on the ground that the Examiner has not met the burden of demonstrating that the entire breadth and scope of the claims is allegedly not enabled. Just as in case of the written description requirement, the burden is again on the Examiner, as required by *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). MPEP specifically states that a presumption of enablement exists. MPEP § 2164.04. It is respectfully submitted that in this case the Examiner has not met the burden of demonstrating the alleged lack of enablement.

The legal standard for determining the adequacy of enablement is well established. To be enabling, "the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." *Genentech Inc. v. NovoNordisk* 108 F.3d 1361, 42 USPQ2d 1001 (Fed. Cir. 1997). The Applicants submit that the specification does comply with the enablement requirement.

The Examiner's grounds for this rejection are not completely clear. For instance, the reference to the "albumin-binding domain asparagines mutants" seems to be misapplied. Nevertheless, it appears that the gist of the Examiner's justification for the lack of enablement rejection is the fact that the claims allegedly include an "infinite number of methods for producing and/or using an infinite number of structural variants (i.e., activity based probes)." (Page 14, first paragraph of the Office Action). As the Applicants explained before, the probes to be used are well-defined in the specification. Particularly, the examples of a functional group F and of moieties "X" and "R" that can

be included in the probe are clearly defined in the specification and are provided above in this response. Also above it has been demonstrated that the probes of the invention can be used with a variety of target proteins, not just with class I aldehyde dehydrogenase. Further guidance is provided in the specification with regard to with respect to the selection of the target proteins. The specification provides at page 32, paragraph [0114]:

> "For many of the enzyme genera, functionalities are known that do not significantly react with enzymes of other genera, particularly non-enzymatic proteins and enzymes that have different reactive sites. It is also desirable that the functionality does not react with inactive target enzyme."

The specification goes on to teach the examples of inactive target enzymes. Furthermore, the specification teaches how to select an appropriate functional group for protein target, e.g., in paragraph [0102], page 27 of the original specification:

> A "chemically reactive group" is a moiety including a reactive functionality that does not react efficiently with the generally available functional groups of proteins, e.g. amino, hydroxy, carboxy, and thiol, but will react with a functionality present in a particular conformation on a surface. In some situations the reactive functionality will serve to distinguish between an active and an inactive protein. In other situations, the conformation of the chemically reactive group will bind to the specific conformation of the target protein(s), whereby with a slowly reactive functionality or one that requires activation, the predominant reaction will be at the active site. For example a photoactivatable group may be used such as a diazoketone, arylazide, psoralen, arylketone, arylmethylhalide, etc. any of which can bind non-selectively to the target protein, while the probe is bound to the active site. Olefins and acetylenes to which are attached electron withdrawing groups such as a sulfone, carbonyl, or nitro group may be used to couple to sulfhydryl groups."

Next, the Examiner questioned whether one example provided in the specification is sufficient. The Applicants point out that the specification contains seven examples, not one. In addition, it is established that providing at least one method for making and using the invention is enough to satisfy the enablement requirement, so long as the example is reasonably correlated to the entire scope of the claim. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The examples provided in the specification teach how to synthesize specific fluorophosphonate probes, and how to carry out every step of the method of the invention. Thus, the examples are reasonably correlated to the entire scope of the claim, which does include using such probes in the manner described in the examples. Accordingly, under the *Fisher* standard, the enablement requirement has been met.

To summarize, it is respectfully submitted that the rejection of claims 12, 14, 16-18, and 20-24 under 35 U.S.C. § 112, first paragraph, as allegedly lacking an enabling disclosure, is not properly applied. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

C. Rejection Under 35 U.S.C. 102(b)

Claims 12, 14, 16, 20, and 21 have been rejected under 35 U.S.C. 102(b), as allegedly being anticipated by Purohit et al. (*Biochemistry*, 1995, *34*, 11508-11514). Claims 12 and 14 recite using "a combinatorial chemical library comprising **a plurality of members** of the formula R* (F – L) – X" by "combining with said complex mixture of proteins, in an active form and an inactivated form, said combinatorial chemical library..."

Purohit et al. fail to teach using a combinatorial chemical library which includes a plurality of compounds. Purohit et al. describe simple protein inhibition, in particular, the inhibition of sulfatase enzymes, using a single compound belonging to the estrone group, as illustrated by Figure 1 on page 11508, Col. 2 in the Purohit et al. reference.

While using any of compounds (1)-(6) shown by Figure 1 of the reference (e.g., EMATE) is disclosed by Purohit et al., using more than one of them simultaneously is not. Thus, a "plurality of members" limitation recited in each of claims 12 and 14 is not taught by Purohit et al.

Therefore, while the present invention allows profiling classes of proteins in a sample on the basis of changes in protein activity rather than simply variations in protein level, what is described in Purohit et al. merely teaches protein inhibition but does not provide for differentiating a complex mixture of proteins on the basis of activity.

Accordingly, each of claims 12 and 14 is patentably distinguishable over Purohit et al. Each of claims 16, 20, and 21 depends on claim 14 and is consequently patentably allowable for at least the same reason. Reconsideration and withdrawal of the rejection of claims under 35 U.S.C. 102(b) are respectfully requested.

D. Rejection Under 35 U.S.C. § 103(a)

Claims 12, 14, 16-18, and 20-24 have been rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Gygi et al. (*Nature Biotechnology* , 1999, 17(10):994-999), Liu et al. (*PNAS*, 1999, 96(26):14694-14699), and Bogyo et al. (*PNAS*, 1996, 94, 6629-6634). This rejection is respectfully traversed. None of the cited references, either alone or in combination, disclose or suggest the methods of the present invention.

With respect to claims 12 and 14, Gygi et al. fail to teach "a combinatorial chemical library comprising a plurality of members of the formula R* (F – L) – X," recited in claims 12 and 14. Instead, Gygi et al. treat two separate protein samples with an isotopically light reagent and an isotopically heavy reagent, respectively (page 994, left column, lines 16-17).

Further with respect to claim 12, Gygi et al. fail to teach that

> "conjugates in said active complex mixture absent in said inactivated complex mixture are comprised only of active proteins reactive with members of said chemical combinatorial library,"

as recited in claim 12. Instead, the protein mixture described in Gygi et al. is denatured, in which mixture all protein structure and activity have been destroyed. Indeed, Gygi et al. specifically teach that their "samples are combined and enzymatically cleaved to generate peptide fragments..." (page 994, left column, lines 18-19). Thus, not only do not Gygi et al. disclose that the "active proteins reactive with members of said chemical combinatorial library," as recited by claim 12, they actually teach away from using active proteins by requiring that the proteins should be denatured. In contrast, the probes set forth in the present invention react with an active site of a protein.

Accordingly, it is respectfully submitted that Gygi et al. does not disclose or suggest the methods of the present invention. Liu et al. and Bogyo et al., either individually, or in combination fail to cure the deficiency of Gygi et al. Liu et al. teach that fluorophosphonate-biotin can be used for activity-based protein profiling. Bogyo et al. teach using the probes with sulfonyl groups, e.g., those derived from vinyl sulfones. This is all that is disclosed by Liu et al. and Bogyo et al., respectively. There are no teachings in these references providing for the above-discussed elements of claims 12 and 14 that are missing from Gygi et al.

Referring to the *In re Keller* and *In re Merck* cases, the Examiner correctly stated that attacking the references individually cannot be used to show non-obviousness, when the 103(a) rejection is based on their combination. Yet, the Applicants respectfully remind the Examiner that regardless of whether an individual reference or a combination is used, to have a proper 103(a) rejection every limitation of the claim has to be disclosed or suggested. Since it is clearly shown by the foregoing analysis that at least some elements of claims 12 and 14 are neither present in the Gygi et al./Liu et al./Bogyo et al.

combination nor suggested by that combination, it is submitted that claims 12 and 14 are non-obvious over the cited references.

Additionally, the Applicants respectfully renew their previous argument that Liu et al. is not available as a prior art reference under 35 U.S.C. 103(a) since the subject matter set forth in Liu et al. was derived from the Applicants' own work. The Examiner rejected this argument (page 25, fourth paragraph of the Office Action) because the inventive entity in the present application (Cravat, Sorensen, Patricelli and Adam) is different from the authorship of the Liu et al. reference after the removal of Mr. Liu's name (leaving Cravat and Petricelli). The Examiner's position is incorrect and does not conform to the existing law for the following reasons.

It has been for many years a well established law that a publication that is used as a ground for a 102(a)/103 rejection can be effectively removed if an applicant can file a declaration under 37 C.F.R. 1.132. The declaration must establish that he or she is a sole inventor of the subject matter disclosed in the publication, while the other co-author of the publication was working under the declarant's direction. *In re Katz*, 687 F.2d 450, 215, 215 USPQ 14 (CCPA 1982), MPEP Section 715.01(c). This situation is further discussed in MPEP § 716.10. The Applicants particularly direct the Examiner's attention to the end of MPEP § 716.10, where Example 2 describes the situation identical to the situation in this case.

Example 2 in MPEP § 716.10 analyzes a situation when a reference describing the claimed invention is found, and the author of the reference is different from the applicant. Ordinarily, the reference is proper prior art but can be removed if a 1.132 declaration is filed, stating that the relevant parts of the reference originated with the applicants. In this case, the Examiner found a reference (Liu, Cravatt, Petricelli) that allegedly made claims 12, 14, 16, 18, and 20-24 obvious. The Applicant (Cravatt) declared under Rule 1.132 that the relevant parts of the reference originated with him, and that a co-author of the

reference (Liu) did not contribute to the mental conception of the present invention. Such declaration was submitted to the Examiner in a previous communication. This is enough under MPEP § 716.10 and applicable case law to remove Liu et al. as the reference.

With regard to the Examiner's observation that the Liu et al. reference and the current application have different inventive entities, this makes no difference. It might have had some bearing in case of 103(c) rejection and in some other situations, but not in this case. The legal concept of "inventive entity" is wholly irrelevant in this situation, because the cited references are not patent documents but rather are articles; therefore, there is no "inventive entity" in the Liu et al. reference.

To summarize, after the removal of Mr. Liu's name, the reference has only two authors who contributed to the present invention. These two authors are also inventors and are two of the applicants. There is nobody else from whom the invention could be possibly derived. It makes no difference that the application has two additional inventors. This is so because the proper rejection here can be based only on "by others" clause of 102(a), and the Cravatt/Petricelli entity is not "others" vis-à-vis the Cravatt/Petricelli/Sorensen/Adam entity.

Consequently, claims 12 and 14 are shown to be patentably distinguishable over the cited art. Claims 16, 18, and 20-24 depend on claim 14 and are patentable for at least the same reasons. Accordingly, reconsideration and withdrawal of the rejection of claims 12, 14, 16-18, and 20-24 are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved, the Examiner is requested to contact the undersigned at the telephone number given below so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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Lisa A. Haile, J.D., Ph.D.
Registration No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

GRAY CARY WARE & FREIDENRICH LLP
4365 Executive Drive, Suite 1100
San Diego, California 92121-2133
USPTO Customer Number 28213